Depression Predicts Mortality Following Cardiac Valve Surgery

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Background. **Depression is associated with mortality in several cardiovascular populations, but has not been evaluated in patients undergoing cardiac valve surgery. Because identifying nonsurgical mediators of survival is important for accurate risk adjustment and the development of interventions to improve outcomes of care, we evaluated the hypothesis that depression predicts mortality following cardiac valve surgery.**

Methods. **This prospective cohort study enrolled 648 patients undergoing valve surgery at 14 Veteran Administration hospitals. A preoperative mental health inventory (MHI) depression screen was performed in all patients and patients were classified as depressed or not depressed using the standard MHI cutoff score of less than or equal to 52. Multivariable logistic regression was used to evaluate the association between depression and 6-month all-cause mortality, adjusting for other clinical risk variables.**

Results. **Overall, 29.2% (189/648) of the patients were depressed at baseline. Depressed patients were younger, more frequently had New York Heart Association class III/IV symptoms, and more likely required emergent surgery, preoperative intravenous nitroglycerin, or intraaortic balloon pump. Unadjusted 6-month mortality was 13.2% for depressed patients compared with 7.6% for nondepressed patients ($p = 0.03$). In multivariable analyses, depression remained significantly associated with mortality (odds ratio 1.90; 95% confidence interval 1.07 to 3.40, $p = 0.03$). These findings were consistent across subgroups of patients undergoing aortic valve replacement, mitral valve replacement and valve replacement without coronary artery bypass graft.**

Conclusions. **Preoperative depression is an independent risk factor for mortality following cardiac valve surgery. Depression screening should be incorporated into preoperative risk stratification, and future studies are warranted to determine if preoperative or postoperative interventions to treat depression can improve outcomes.**

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There has been a steady increase in the number of cardiac valve surgeries over the last 20 years in the United States, with more than 80,000 procedures performed in the year 2000 [1]. Operative mortality varies depending on the position of the valve, concomitant coronary artery bypass graft (CABG) surgery, and urgency of the procedure, ranging from 4.3% for isolated aortic valve replacement to 18.8% for multiple valve and CABG surgery [2]. Preoperative assessment of mortality risk is routinely performed in patients undergoing valve surgery and factors such as emergency/salvage procedure, recent myocardial infarction, reoperation, renal failure, and older age are associated with increased mortality risk [3, 4].

In addition to the established clinical factors, there may be utility in assessing novel predictors of survival for accurate risk adjustment and the development of interventions to improve care. Depression is common among patients with cardiovascular diseases, with a prevalence as high as 27% to 47% among patients undergoing CABG surgery [5–7]. For CABG surgery patients, preoperative depression has been associated with significant postoperative morbidity and mortality [6, 8–10]. To date, however, depression has not been evaluated as a predictor of mortality for cardiac surgery in nonischemic states such as valve surgery. The objective of this study was to determine the prevalence of preoperative depression and whether preoperative depression was independently associated with mortality following valve surgery.

Patients and Methods

Patients

Patients were enrolled in the Department of Veteran's Affairs Cooperative Study in Health Services #5, "Processes, Structures, and Outcomes of Care in Cardiac Surgery" (PSOCS), a multicenter, prospective, observational study investigating the linkages between processes

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Table 1. Preoperative Clinical Risk Variables of the Study Population (N = 648)[a]

Variable	Depressed % (n = 189)	Not Depressed % (n = 489)	*p* Value
Age, mean (SD)	63.9 (11.2)	66.2 (9.4)	0.01
Male gender	96.3	98.3	0.13
Body surface area m^2/kg, mean (SD)	1.9 (0.20)	1.9 (0.19)	0.28
Prior heart surgery	19.6	17.0	0.43
Hypertension	54.0	47.5	0.13
NYHA functional class III or IV	67.7	59.7	0.06
CCS angina functional III or IV	30.2	31.8	0.68
Myocardial infarction within 7 days	0.5	0.2	0.52
Surgical priority, urgent or emergent	10.0	4.1	<0.01
Intravenous nitroglycerin	4.7	1.9	0.05
Intra-aortic balloon pump	1.5	0.2	0.04
ST-segment depression on preoperative ECG	15.3	12.9	0.41
Left ventricular ejection fraction < 0.45	28.3	28.5	0.17
Left main coronary artery disease	7.9	8.2	0.89
3 vessel coronary artery disease	12.7	13.1	0.90
Chronic obstructive pulmonary disease	14.8	14.2	0.83
Serum creatinine mg/dL, mean (SD)	1.3 (0.9)	1.3 (0.7)	0.40
Diabetes	16.9	19.2	0.50
Cerebrovascular disease	20.6	16.8	0.24
Peripheral vascular disease	28.0	22.2	0.11

[a] Data are expressed as percentages unless otherwise indicated.

CCS = Canadian Cardiovascular Society; ECG = electrocardiogram; NYHA = New York Heart Association; SD = standard deviation.

and structures of care and risk-adjusted outcomes. Details of the study have been published previously [11]. Seven hundred thirty-four variables representing patient-related risk factors, processes, structures and outcomes of care were collected on a representative sample of 4,969 patients who underwent cardiac surgery at 14 Veteran's Administration (VA) medical centers between September 1992 and December 1996. Clinical and procedural data were prospectively collected by patient interview and chart review within 72 hours before surgery by full-time, trained research nurses located at each of the 14 sites. The baseline mental health inventory (MHI) depression screen was provided to the patients for self-administration. If a patient was unable to complete the MHI, the survey was completed by means of a personal interview with the research nurse.

The patients included in the current analysis were all those enrolled in the PSOCS who underwent valve

Table 2. Univariate Predictors of 6-Month Mortality

Variable	Odds Ratio	95% Confidence Intervals	*p* Value
Intraaortic balloon pump	10.1	1.40–73.0	0.02
Intravenous nitroglycerin	4.02	1.38–11.7	0.01
Chronic obstructive pulmonary disease	3.53	1.95–6.36	0.03
Hypertension	2.39	1.35–4.22	<0.01
Surgical priority, urgent or emergent	2.37	0.99–5.65	0.05
Peripheral vascular disease	2.15	1.23–3.74	<0.01
ST-segment depression on preoperative ECG	2.11	1.11–4.02	0.02
Valve plus CABG surgery	2.11	1.23–3.65	<0.01
Cerebrovascular disease	1.95	1.07–3.56	0.03
NYHA functional class III or IV	1.94	1.06–3.56	0.03
Depression	1.85	1.07–3.18	0.03
Age, per 10-year increment	1.85	1.32–2.61	<0.01
Diabetes	1.69	0.92–3.11	0.09
Serum creatinine, per 0.83 mg/dL increment	1.40	1.16–1.71	<0.01

CABG = coronary artery bypass graft; ECG = electrocardiogram; NYHA = New York Heart Association.

Table 3. Multivariable Predictors of 6-Month Mortality After Cardiac Valve Surgery

Variable	OR	95% CI	*p* Value
Chronic obstructive pulmonary disease	3.42	1.84–6.38	<0.01
Depression	1.90	1.07–3.40	0.03
Hypertension	1.89	1.04–3.42	0.04
Age (per 10-year increment)	1.83	1.28–2.64	<0.01
Serum creatinine (per 0.83 mg/dL increment)	1.39	1.14–1.70	<0.01

CI = confidence interval; OR = odds ratio.

surgery with or without concomitant CABG and completed a preoperative MHI. Of the 902 valve surgery patients enrolled in the PSOCS study, 648 (71.8%) completed a baseline MHI. The primary reason for missing the baseline MHI was urgent or emergent surgical priority. Therefore, the study population included predominantly elective patients. Excluded patients were more likely to have recent myocardial infarction, Canadian Cardiovascular Society angina (CCS) class III or IV, ST-segment depression on preoperative electrocardiogram, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), or to have required preoperative intravenous nitroglycerin or intraaortic balloon pump.

Variables

The primary predictor variable of interest was depression based on the MHI depression screen. The MHI-5 is a five-item measure developed for the Rand Health Insurance Experiment, and has been found to be a reliable measure with strong convergent and discriminatory validity [12–14]. The MHI-5 has been validated against the reference standard for depression, the structured psychiatric interview [15]. When compared to the diagnostic interview schedule, the MHI-5 demonstrated substantial capability for detecting depression with an area under the receiver operator curve of 0.89 [12]. Responses to the five items are summed and the scores are converted to a 0 to 100 scale, with higher scores indicating better mental health. Patients can be categorized as depressed or nondepressed based on an established cutoff score of equal to or less than 52 [16].

Candidate preoperative clinical variables for risk-adjustment in the mortality analyses were derived from the published literature in both VA and non-VA populations [2–3, 17]. These demographic, cardiac, and noncardiac variables are listed in Table 1.

The outcome variable was all-cause mortality within 6 months of the date of valve surgery. Vital status was determined by the research nurses and confirmed using the Department of Veterans Affairs Beneficiary Identification and Record Locator System. This method is comparable to the National Death Index in terms of completeness of the assessment for mortality in the VA population [18].

Statistical Analyses

Baseline characteristics of the depressed and nondepressed patients were compared using the χ^2 test for categorical variables and the *t* test for continuous variables. Univariate logistic regression was performed to assess the unadjusted association between candidate independent variables (depression and the clinical risk variables listed in Table 1) and 6-month mortality. Multivariable logistic regression with backward selection ($p \leq 0.10$ to enter; $p < 0.05$ to remain in model) was used to assess the independent relationship between depression and 6-month mortality, adjusting for the clinical risk variables.

Secondary analyses were performed to evaluate the relationships between depression and mortality in subgroups of patients undergoing mitral valve replacement, aortic valve replacement, and valve replacement without concomitant CABG. Two-way interaction terms between depression and each of these subgroups were evaluated in the multivariable model.

Furthermore, because missing survey data can potentially bias risk models (ie, selection bias from survey nonresponders), propensity score analysis was performed to assess for bias due to missing questionnaires [19, 20]. A propensity score was derived for each patient, estimating the likelihood that a patient would complete a baseline MHI depression screen. This propensity score was then used in the multivariable models for risk adjustment. Analyses were performed using the SAS statistical package version 8.0 (SAS Institute, Cary, NC). The study was approved by the Colorado Multiple Institutional Review Board.

Results

Baseline characteristics of the study population are listed in Table 1. Compared to nondepressed patients, depressed patients were younger and more likely had New York Heart Association (NYHA) functional class III or IV symptoms. In addition, depressed patients more likely required urgent or emergent surgery, preoperative intravenous nitroglycerin or peroperative intraaortic balloon pump.

Unadjusted 6-month mortality was 13.2% for depressed patients and 7.6% for nondepressed patients. Univariate predictors ($p \leq 0.10$) of 6-month mortality are shown in Table 2. In unadjusted analysis, depression was associated with 6-month mortality with an odds ratio (OR) of 1.85 (95% confidence interval [CI] = 1.07–3.18; $p = 0.03$).

In multivariable analysis, depression remained a statistically significant predictor of 6-month mortality (OR 1.90; 95% CI 1.07–3.40; $p = 0.03$). Other statistically

significant predictor variables for mortality in this model included history of COPD, history of hypertension, older age, and higher serum creatinine (Table 3). The association between depression and mortality was consistent across subgroups of patients undergoing aortic valve replacement, mitral valve replacement, and valve replacement without CABG (p value for interaction between depression and surgical subgroups > 0.10). Finally, propensity score analyses assessing for bias due to missing questionnaires did not alter our primary findings.

Comment

The objective of this study was to determine the prevalence of preoperative depression and whether depression was predictive of mortality following valve surgery in a multicenter cohort of VA patients. We found that nearly 1 in 3 patients had significant depressive symptoms at baseline. Furthermore, preoperative depression was an independent predictor of 6-month mortality, with a 1.9-fold increased odds of death, even after adjustment for the traditional clinical risk variables. This finding was consistent across subgroups of aortic valve replacement, mitral valve replacement, and valve replacement without CABG.

The prevalence of depressive symptoms before cardiac valve surgery found in this study (29.2%) can be compared with previous studies reporting a prevalence of active depressive symptoms of 27% to 47% in patients undergoing CABG surgery, 30% in patients with heart failure, and 17% to 65% in patients who have suffered a myocardial infarction [5–7, 21, 22]. This study therefore adds to the existing evidence that depression is particularly common in cardiovascular populations, with a significantly higher prevalence than is found in general medicine populations and approximately threefold higher prevalence than the general population [23, 24].

Prior studies have focused on the link between depression and cardiac surgery for ischemic heart disease, ie, coronary artery bypass and these studies have demonstrated that depression can have a significant impact on outcomes after CABG surgery. Pre-CABG depressive symptoms have been associated with postoperative depression, continued surgical pain, and failure to return to previous activities at 6 months [6, 10]. In addition, depression before CABG surgery has been associated with longer lengths of stay, higher rates of hospital readmission within 6 months, and a greater need for repeat procedures [8]. Finally, depressive symptoms have been associated with increased short- and long-term mortality after CABG surgery [5–7]. This study examines the impact of depression on mortality following cardiac surgery for nonischemic states, such as valve surgery. The findings of this study, coupled with the existing literature, highlight the significant impact of depression on outcomes after cardiac surgery, including both CABG and valve surgery.

Our finding that preoperative depression is an independent predictor of mortality following valve surgery is also consistent with previous studies demonstrating that depression is associated with increased mortality and morbidity among patients with other cardiovascular conditions. For example, depressive symptoms are independently predictive of mortality up to 5 years after acute myocardial infarction, and have also been shown to predict major cardiac events following unstable angina [25, 26]. In heart failure populations, depression is associated with increased rates of mortality and rehospitalization for heart failure, and has been shown to predict worsening of heart failure symptoms and health-related quality of life [21, 27]. Furthermore, depressive symptoms at the time of cardiac catheterization are associated with an increased risk of cardiac death over long-term follow-up (eg, 19 years) [28]. These studies underscore the significance of depression as a risk factor for adverse outcomes among patients with various cardiovascular conditions.

The results of this study, taken together with previous studies of CABG surgery patients, highlight the importance of considering the assessment of preoperative depression among cardiac surgery patients both for the purposes of refining risk stratification and for identifying potential opportunities to improve patient care. Among patients with similar clinical risk profiles, depression identifies higher-risk patients before the operation. Furthermore, treatment of depression among patients with cardiovascular diseases may lead to improved outcomes. Although this has not been assessed in cardiac surgical populations, two studies have assessed depression treatment in patients after unstable angina or myocardial infarction. In the SADHART study, there was a nonsignificant trend towards a reduction in mortality, MI, angina, heart failure and a composite of these endpoints in patients post-MI treated with the antidepressant sertraline [29]. In posthoc analysis of the ENRICHD study, patients receiving a selective serotonin reuptake inhibitor to treat depression had lower cardiovascular and all-cause mortality [30]. Thus, the existing evidence suggests that the routine assessment of depression among patients considering cardiac surgery may be useful. Furthermore, future studies to determine if preoperative or postoperative interventions to treat depression can improve outcomes for such patients are warranted.

Although the specific mechanisms underlying depression and increased mortality after valve surgery are not known, there have been several proposed links between depression and adverse cardiovascular outcome [5, 24]. These potential mechanisms include direct influence on health-related behaviors, such as smoking, poor compliance with treatment, or inactive lifestyle and multiple potential pathophysiologic pathways such as effects on myocardial perfusion, autonomic nervous system regulation, platelet activation, hypothalamo-pituitary-adrenal axis activity, and inflammatory processes [5]. Some of these mechanisms may explain the association between depression and increased mortality after valve surgery,

but further studies are needed to clarify these potential associations.

Several issues should be considered in the interpretation of this study. The population was largely a male veteran population, which may limit the generalizability of our findings to other settings. Second, the population included only patients with a preoperative MHI depression survey, conferring a bias toward more elective, lower-risk patients. However, it can be logistically difficult to obtain a patient survey on urgent or emergent cases, and such patients often have pressing indications for valve surgery. Our study population may therefore reflect a realistic population in which one may consider baseline depression screening as part of the preoperative evaluation. Furthermore, we used propensity score analysis to adjust for potential bias due to missing questionnaires, and this adjustment did not alter our primary findings.

In conclusion, this study demonstrates that depression was an independent predictor of mortality following valve surgery. Depression screening should be considered as part of preoperative risk stratification, and future studies are warranted to determine if preoperative or postoperative interventions to treat depression can improve outcomes for such patients.

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